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Review

Domain interplay concept in animal models of neuropsychiatric disorders: A new strategy for high-throughput neurophenotyping research

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Abstract

Genetic and environmental factors play a key role in psychiatric disorders. While some disorders display exceptionally high heritability, others show gene × experience × personality interactions, contributing complexity to psychiatric phenotypes. As some brain disorders frequently overlap and co-occur (representing a continuum or spectrum of phenomena), modern psychiatry is shifting from "artificial" heterogeneity to the recognition of common elements in the pathogenesis of emotional, personality and behavioral disorders. Genetic animal models of these disorders represent an important direction of research, and are widely used to explore the role of different genes in brain mechanisms. Several concepts (such as endophenotypes, gene × environment interactions, and cross-species trait genetics) have been suggested for animal experimentation in this field. Here we develop a new concept based on targeting the complex interplay between different behavioral domains, meant to foster high-throughput phenotyping and integrative modeling of psychiatric disorders.
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Keywords: Genetic animal models; Brain disorders; Behavioral/psychiatric phenotypes; Domain interplay; Comorbidity; Gene × environment interaction; Mutant and transgenic animals

Contents

1. Introduction

Animal experimental models of brain disorders represent a valuable tool in refining the existing, and developing new, neuropsychiatric theories [1,16,33–35,39,40]. Various genetic animal models, based on selectively bred, hybrid, gene-targeted or transgenic animals, are widely used for screening psychotropic drugs, testing neurobiological hypotheses and finding candidate genes for human brain disorders [9,15,38,41,71].

Several currently accepted concepts of behavioral phenotyping are summarized in Fig. 1A. Some of them focus on direct effects of individual genes, their networks and gene × environment (G × E) interactions in the regulation of animal and human behaviors [12–14,30,48,53,65]. Endophenotyping approach seeks to use relatively simple "symptoms" or biological phenomena as markers for complex behaviors (syndromes) [27,28,32,66,73]. Recently, Kas et al. [47] developed an interesting concept of "cross-species trait genetics" (vs. complex syndrome genetics) to clarify genotype–phenotype relationships and foster translation of animal behaviors into models for human psychiatric disorders (Fig. 1A). However, recent paradigm shifts in modern psychiatry, refocusing from

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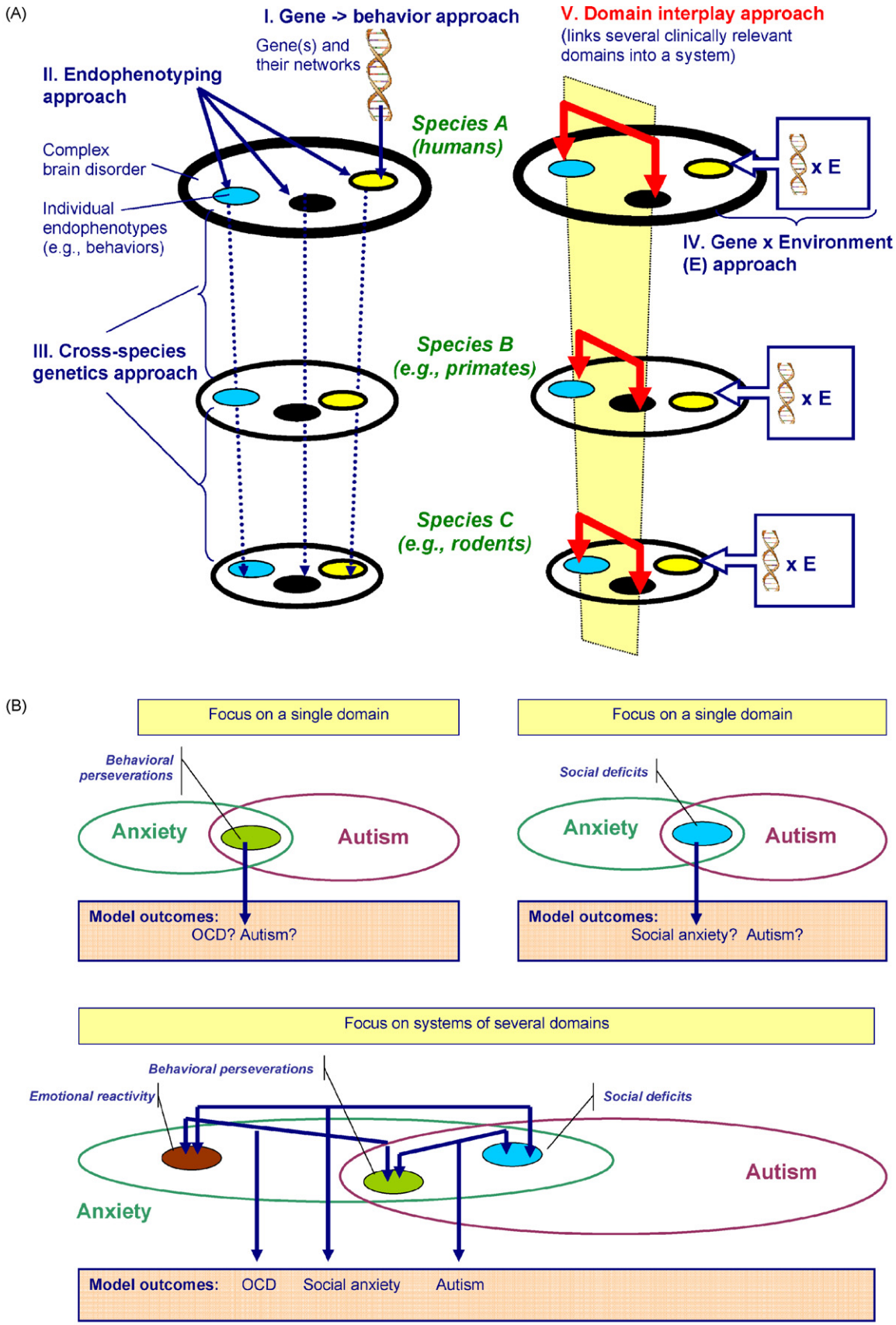

Fig. 1. Domain interplay strategy for neurophenotyping research. (A) Current strategies in genetic modeling of a complex human psychiatric disorder (indicated as large black-rimmed circles) in experimental models using different species. Individual domains are presented as small circles within a complex disorder. Domain interplay approach focused on linking interplaying domains into a system (marked with bold arrows; also in panel B), then consistently modeling this system across different species (yellow plane). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

individual 'specific' diagnoses to a more integral continuum [2,6,8,18,50] with common genetic and environmental determinants [37,38,45], require additional phenotyping approaches to more completely evaluate newly appreciated disorder overlaps [46].

To further optimize genetic animal modeling of neuropsychiatric disorders, here we develop a domain interplay concept that is based on analyses of clusters of behavioral endophenotypes or domains, as well as on their interplay and dynamics (rather than simply focusing on specific individual behaviors, genes or domains of interest; see further). The present concept is different from all previously known phenotyping theories, as it emphasizes the importance of assessing *systems of domains* as a highly valid strategy to unravel complex neuropsychiatric phenotypes. Offering a principally new phenotyping strategy (Fig. 1A and B), and being consistent with recent integrative trends in clinical psychiatry, this concept is expected to further stimulate the development of genetic animal models and improve their translation into neuropsychiatric/behavioral disorders.

2. Problems with animal models

Specialists in the field of biological psychiatry know that animal models of brain disorders are not easy to develop and perhaps even more difficult to interpret [9,15,46,71]. Since experimental models often fail to reproduce complex multisyndromal human disorders, one solution may come from an in-depth focus on analogous phenotypes, functional polymorphisms and conserved gene functions [47]. However, despite the fact that such analogies would indeed strengthen face validity of an animal model, *real* brain disorders do not necessarily have these analogies. Indeed, not all candidate genes show functional polymorphisms, or have functional analogs in men and mice (e.g. [29]). Moreover, behavioral and physiological phenotypes across different species may sometimes lack overt analogies, or show false similarity, with mimicking (at a phenocopy level) vs. modeling a "true" psychiatric state. For example, rodent tail suspension or forced swim behaviors are not simple analogues to human depression [57,69], whereas temperature responses to some serotonergic agents are opposite in direction in rats vs. mice [42]. Unlike humans, most animals are macrosmatic, and the role of olfactory stimuli in their behavioral models is by far more important [43,52]. Collectively, these inter-species differences yield conflicting behavioral, neurogenetic or pharmacological results, and seem to complicate markedly their translation into human phenotypes.

Species differences in the complexity of CNS or cognitive involvement in behavior further complicate potential translation of human symptoms into animal tests based on analogous phenotypes [37,45]. Moreover, as some neuropsychiatric disorders are characterized by complex G × E interactions [12,14,65], cross-species analysis of environmental inputs (which may also differ across species) is needed in order to more fully assess trait genetics in animal models. Other related problems with genetic modeling are species-specific differences in behavior, epigenetic factors and inter-individual variability, as well as ontogeny of brain disorders (sometimes limited to specific stages of brain development, whose timing may also differ across species); see Refs. [15,46,71] for discussion.

Finally, behavioral phenotyping may have problems with correct dissection of disorder-specific domains vs. comorbidity. For example, mild forms of anxiety and depression are clinically similar, commonly co-occur, and most likely share common neurobiological mechanisms and genetic determinants (see Ref. [45] for detailed review). Likewise, addiction and drug abuse are commonly comorbid with human depression and anxiety, also sharing some common genetic determinants [19,20,24,25,54,55]. Obsessive-compulsive disorder (OCD) and OCD spectrum disorders (OCSD) are characterized by numerous anxiety-related phenotypes, cognitive and behavioral inhibition deficits, and frequent comorbidity with depression, addiction and other psychiatric disorders [4,5,22,23]; Fig. 2. Taken together, these data raise the possibility that a *combination* of several distinct but interacting domains may be mistaken for a clinical (endo)phenotype of interest. While a similar problem may also occur in animal modeling using traditional phenotyping approaches (Fig. 1B), a closer in-depth analysis of different domains and their *interplay* may be needed for further clinically relevant genetic experimental modeling of neuropsychiatric disorders.

3. Domain interplay: the concept and selected examples

Why is domain interplay important? Consider, for example, anxiety and autism—two complex multifaceted psychiatric disorders, dramatically affecting human populations [21,26,58,60,62,67,68,72]. Their high comorbidity, common genetic determinants and some clinical manifestations, as well as partial effectiveness of serotonin reuptake inhibitors and some anxiolytics to treat both disorders, raise the possibility that these two disorders may overlap in the "social interaction" domain [10,11,17,58] (Fig. 1B). However, this also implies that simply mimicking social deficits alone and across species may not allow a reliable dissection of experimental anxiety and autism. In contrast, the use of several domains makes these efforts more specific. For example, genetic models focusing on social interaction deficits accompanied by global behavioral inhibition and reduced exploration and/or increased emotionality (anxiety domain) may be relevant to generalized anxiety pathogenesis (Fig. 1B). In contrast, animals with both social deficits and anxiety are most likely relevant to social anxiety disorder. Models showing both emotionality and OCD-like behavioral perseverations (but normal social ability) seem to target OCDS, whereas animals with impaired social behavior and increased behavioral perseverations may be more relevant to autism [10,17,26,58] (also see Figs. 1B and 2 for graphic illustrations). In a similar vein, mimicking an anxiety-depression pathogenetic continuum in animal genetic models (in addition to focusing on the two disorders as static "points", as do most of the existing behavioral models) may be a key strategy to better our understanding of these serious stress-evoked disorders [46], whose overlap and comorbidity have already been mentioned.

Can we improve our present neurophenotyping strategies? Fig. 1A summarizes the domain interplay concept developed

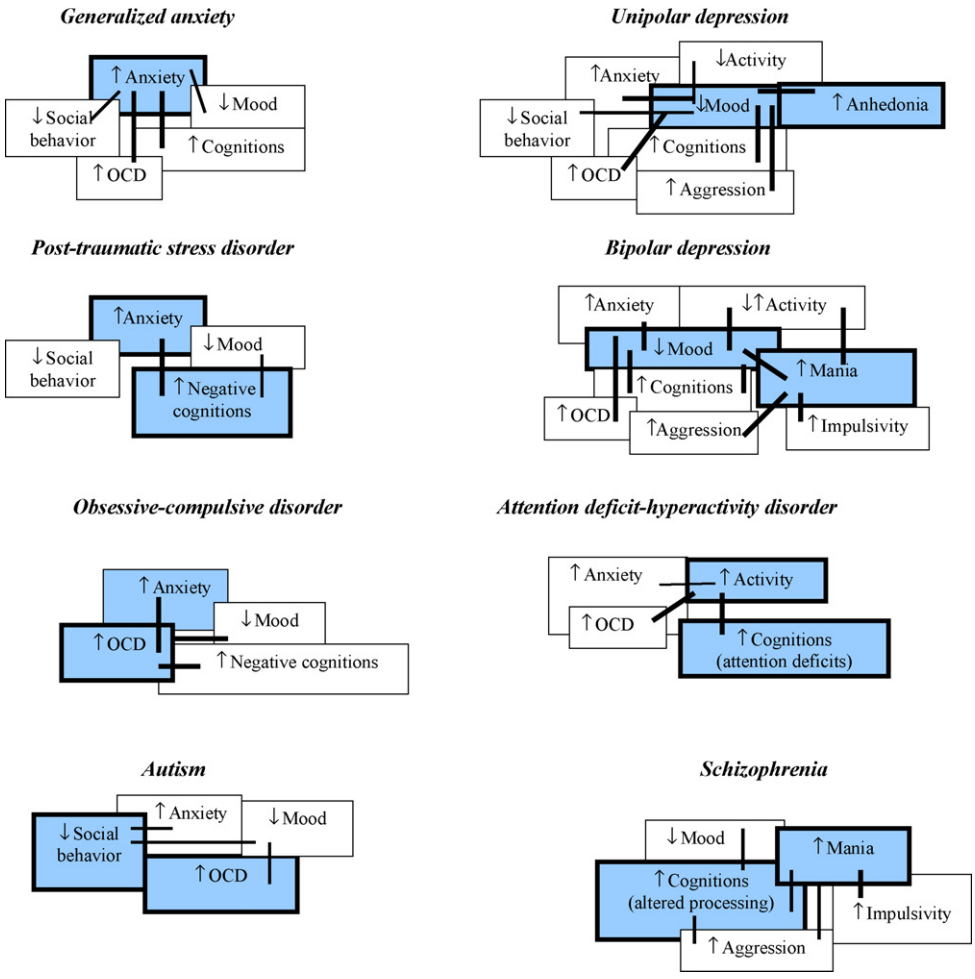

Fig. 2. Examples of behavioral domains interplay in different genetic models of brain disorders (core disordered domains, based on clinical data, are marked with color; ↑ activation; ↓ inhibition). Interplaying domains (to be modeled in animal models) are interconnected. Experimental models that simultaneously target more interplaying domains will have higher construct validity. OCD, obsessive-compulsive disorder.

here. Briefly, it postulates that if a human disorder A leads to disorder B, co-occurs with it, increases its risks or worsens pathogenesis and treatment outcome, then we need not only to develop genetic models that mimic disorders A and B, but also to search specifically for those models where A-like phenotype will exacerbate B-like phenotype, or increase the probability of the occurrence of B. This approach may also be well-combined with above-mentioned cross-species trait genetics approach [47], as interplay between two domains (or traits) *across* different species (Fig. 1A) will most likely reflect a core feature of pathogenesis, and therefore, further strengthen the construct validity of the model in question.

Importantly, by "interplay" between different domains we should also understand possible negative interrelationships. For example, if domain A precludes (or minimizes risks of) domain C, we need to develop animal genetic models that will reflect this phenomenon (e.g., mutant mice with A-like behavior will be less prone to display C-like behaviors, and vise versa).

Finally, since construct validity is the main quality of animal models of brain disorders, domain interplay approach that mimics pathogenetic processes in detail, would lead to improved construct validity of models in question. While parallel assessment of several domains has long been recognized in behavioral phenotyping of genetically modified animals, it is becoming crucial to have genetic models that would focus specifically on overlapping domains (viewing them as a pathogenetic process, or "system"; Fig. 1A and B), and parallels this overlap to human clinical data.

Fig. 2 summarizes disordered domains and their interplay in different behavioral models of several common neuropsychiatric disorders, representing targets for domain interplay-oriented phenotyping research. Animal models that mimic interplay of these disordered domains in a way presented in Figs. 1 and 2 will have higher construct validity and clinical relevance, strengthening the utility of our approach in phenotyping of genetically modified animals and translating animal behaviors into models of human psychiatric disorders. Several further examples may illustrate the developing utility of domain interplay-oriented phenotyping research.

Numerous clinical and animal studies have implicated serotonin, serotonin transporter (SERT) and brain-derived neurotrophic factor (BDNF) in brain pathogenesis. Serotonergic system and BDNF not only exert their modulatory effects on behavior, but also interact at genetic and molecular levels in the

regulation of normal brain mechanisms and neuropsychiatric phenotypes [56,63,64,70]. Human variants at both the SERT and BDNF gene loci have been implicated in affective disorders, OCD and polysubstance abuse liability [31,36,59,61,67], strengthening the importance of studying interactions between these genes using animal experimental models. Consider domain-oriented research of obesity in SERT−/− or BDNF+/− mice. While an assessment of body weight phenotype alone will not clarify potential mechanisms of their obesity, a focus on its relation to other domains (e.g., food intake in BDNF+/− mice [51] or hypoactivity in SERT−/− mice [39]) may be useful, suggesting that obesity is most likely pathogenetically linked to overeating in BDNF mice and hypoactivity in SERT−/− mice. Recent studies have further confirmed the importance of analysis of interplay between obesity and other domains, such as anxiety, aggression and depression [49]. Indeed, patients with eating disorders often manifest associated anxious and aggressive symptoms, while dietary restriction (that increased levels of serotonin in the frontal cortex of BDNF+/− mice) reduced their obesity, anxiety and aggression [49]. These findings support the interplay between obesity and other domains, suggesting that further genetic models targeting this interplay may be necessary to better understand related complex human clinical phenotypes.

In addition to single gene mutant models, an important area of research in biological psychiatry is the use of double mutant models, such as SERT−/− × BDNF+/− mice. For example, double SERT−/− × BDNF+/− mutant mouse data show that reduced BDNF availability during development exaggerates the consequences of absent SERT function, leading to higher obesity and anxiety [59,64]. These double-mutant mice also have greater stress-induced increases in plasma adrenocorticotropic hormone, more aberrant neuronal morphology [64] and poorer performance in radial maze (own unpublished data), compared with single-mutant mice. Such complexity of (endo)phenotypes offers excellent opportunities for modeling interplay between multiple, clinically relevant affected domains.

Likewise, the role of cognitive factors in psychiatric disorders has long been recognized in clinical literature, as they not only accompany brain disorders but also represent a key pathogenetic factor *per se* [37,45]. Over the last years, a number of genes have been implicated in cognitive functions [66,67]. Therefore, cognitive domains and their interplay with non-cognitive domains warrant further scrutiny in genetic animal models of neuropsychiatric disorders. The importance of in-depth assessment of domain interplay has been recently emphasized using a model situation with only two interplaying domains (memory and anxiety or depression) that may lead to multiple alternative states, misinterpretations of which in different tests would generally be unavoidable if only single domains (rather than their interplay) were assessed [44].

4. Concluding remarks

In general, assessment of inter-linked domains in different genetic and behavioral animal models may complement the existing phenotyping concepts (Fig. 1A), and further advance our understanding of psychiatric pathogenesis. As a new phenotyping strategy, domain interplay approach has several clear advantages for genetic modeling of brain disorders. First, assessment of several distinct domains (and their interplay) minimizes the risk of incorrect interpretations of animal behaviors in different genetic models, which is more likely if domains are assessed or mimicked separately.

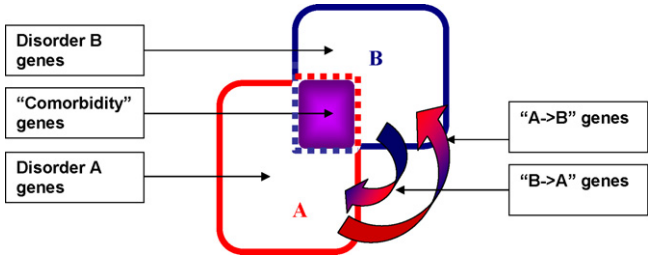

Fig. 3. Genetic and environmental determinants of neuropsychiatric disorders: a model based on two overlapping and comorbid disorders A and B, and five groups of candidate genes potentially involved in their pathogenesis.

Second, a focus on clinically relevant "interplay" aspects of pathogenesis fosters further innovation in animal integrative experimental modeling (based on spectrum-oriented psychiatric theories is modern psychiatry [3,7,18,50]), whose need has been recognized in biomedical research [46]. Third, a focus on dynamic interplay between different domains (in addition to studying individual domains) betters our understanding of pathogenesis of complex brain disorders, their comorbidity, common mechanisms and risk factors. Fourth, this strategy can help predict how altered specific domain(s) may influence other domains in different genetic models, including those not yet fully explored.

Given high comorbidity of psychiatric disorders, our approach may also have an additional "practical" advantage in cases when symptoms are unclear or poorly understood. Indeed, instead of mimicking individual symptoms (whose proper dissection is complicated by comorbidity or poor diagnostic criteria), researchers may target their pathogenic interplay, leading to models with good face and construct validity (reflecting a *real* clinical picture of pathogenesis rather than focusing on unclear details).

Finally, as shown in Fig. 3, modeling brain disorders as systems of *interplaying* domains, not only allows investigators to search for specific candidate genes responsible for individual disorders A or B (which is presently the most common task of psychiatric genetics research), but also to pursue even more far-reaching goals. For example, this approach may help detect genes responsible specifically for comorbidity of these disorders, and also those genes which determine the direction of pathogenesis (i.e., A->B or B->A types of pathogenesis). Understanding that in addition to genetic risk factors of individual brain disorders, there may be specific "comorbidity" genes and "pathogenetic vector" genes (specifically responsible for disorders' overlap) as well as specific "domain" genes and "domain interplay" genes, may help clarify further the genetic linkage data which often yield conflicting results in traditional gene/domain or gene/disorder-oriented studies. Thus, genetic animal models based on targeting different domains and their

interplay can increase our understanding of neural and genetic underpinnings of complex human psychiatric disorders.

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